AF/1615

Attorney Docket # 4961-5RCE

Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Veerappa S. SUBRAMANIAN et al.

Serial No.: 09/933,559

Filed: August 20, 2001

For: Sustained Release Tablets Containing Bupropion Hydrochloride

Examiner: M.P. Young
Group Art: 1615

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Kent H. Cheng
Name of applicant, assignee or Registered Representative

Kent H Cheng
Signature

March 11, 2005
Date of Signature

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APPEAL BRIEF

SIR:

Pursuant to the provisions of 37 CFR 41.37, this brief is being filed together with a check in the amount of $250.00 for the fee and a check in the amount of $65.00 for a one month extension of time. The Notice of Appeal was filed on December 15, 2004.

Any additional fees or charges in connection with this application may be charged to our U.S. Patent and Trademark Office Deposit Account No. 03-2412.

REAL PARTY IN INTEREST

The real party in interest is Kali Laboratories, Inc.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences at the present time.

STATUS OF CLAIMS

Claims 1-17 are pending. All of these claims are being appealed.

STATUS OF AMENDMENTS

There was no amendment subsequent to the final rejection.

SUMMARY OF THE INVENTION

Independent claim 1 relates to a composition in solid form comprising bupropion hydrochloride and an effective amount of carboxyvinyl polymer. The carboxyvinyl polymer acts as both the sole stabilizing agent and the sole controlled release material. As disclosed in the specification, the use of carboxyvinyl polymer as a stabilizer prevents or inhibits the degradation of bupropion hydrochloride. Functioning as a controlled release material, carboxyvinyl polymer controls the duration of the sustained release of bupropion hydrochloride. As the concentration of carboxyvinyl polymer is increased, the duration of the sustained release is also increased.

Independent claim 12 relates to a sustained release tablet comprising bupropion hydrochloride, carboxyvinyl polymer, and lactose. Again, the carboxyvinyl polymer acts as both the sole stabilizing agent and the sole controlled release material.

Independent claim 13 relates to a sustained release tablet comprising bupropion hydrochloride, carboxyvinyl polymer, and microcrystalline cellulose. Again, the carboxyvinyl polymer acts as both the sole stabilizing agent and the sole controlled release material.

Claims 14 and 15 are dependent on claims 12 and 13, respectively. Both claims 14 and 15 disclose the following release rates:

> 30-45% of the Bupropion Hydrochloride in 1 hour,
> 60-80% of the Bupropion Hydrochloride in 4 hours, and
> not less than 85% in 7 hours.

Claims 16 and 17 are dependent on claims 12 and 13, respectively. Both claims 16 and 17 disclose the following release rates:

> 10-25% of the Bupropion Hydrochloride in 1 hour,
> 30-60% of the Bupropion Hydrochloride in 8 hours, and
> not less than 65% in 12 hours.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-17 stand rejected under 35 USC 103(a) as being unpatentable over the combined disclosures of Lowey (U.S. Patent 4,680,323, the '323 patent), Baker et al. (U.S. Patent 4,687,660), and Seth (U.S. Patent 6,033,686).

ARGUMENT

Claims 1, 12, and 13

The '323 Patent discloses a sustained release pharmaceutical carrier **comprising hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and carboxyvinyl**

polymer. As the '323 Patent states, **HPMC is a well known controlled release material** in pharmaceutical formulations (see col. 1, lines 34-45).

The '660 Patent discloses a pharmaceutical controlled delivery system for beneficial agents. The pharmaceutical delivery system comprises a core containing a beneficial agent, an osmotic enhancing agent, and a water-insoluble, water-permeable coating such as cellulose acetate surrounding the core. The beneficial agent can be bupropion hydrochloride.

The '686 Patent discloses a controlled release tablet comprising a core that contains bupropion hydrochloride and conventional excipients, and a coating that consists essentially of water-insoluble water-permeable film-forming polymer such as ethylcellulose. The '686 Patent discloses a method of preparing the composition comprising mixing the constituents and granulating with purified water.

Based on the above-mentioned references, the Examiner stated that a skilled artisan would have been motivated to combine the bupropion HCl of the '660 Patent into the formulation of the '323 Patent in order to impart stability and proper release of the agent. The Examiner further stated that a skilled artisan would have further been motivated to combine the purified water and additional excipients of the '686 Patent in order to better refine the processing and release profile of the active agent. Therefore, the Examiner rejected claims 1-17 as being obvious over the '323 Patent in view of the '660 Patent and further in view of the '686 Patent.

We respectfully traverse. It is our opinion that a *prima facie* case of obviousness has not been established. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143 -§2143.03 for decisions pertinent to each of these criteria.

In the present case, even if a skilled artisan had combined the bupropion HCl of the '660 Patent into the formulation of the '323 Patent, as the Examiner proposed, the formulation would comprise **bupripion HCl, HPMC, HPC, and carboxyvinyl polymer**. Hence, in addition to carboxyvinyl polymer, **at least HPMC would be a controlled release material in the proposed formulation,** which would be different from the formulation of the present invention, which comprises carboxyvinyl polymer as the sole controlled release material. Therefore, as Applicant stated in the response of September 22, 2003, **even if a person of ordinary skill in the art had made the combination as proposed by the Examiner, he or she would not have arrived at the present invention**.

Because the references when combined as the Examiner proposed do not teach or suggest all the claim limitations of the present invention, the Examiner failed to properly establish a *prima facie* case of obviousness. Further, **if the Examiner were to argue that the controlled release material other than carboxyvinyl polymer, for example HPMC, in the proposed formulation may be omitted to arrive at the present invention, Applicants should be informed of the motivation or suggestion, and a reasonable expectation of success for this omission, as required by U.S. law previously cited.** In fact, as MPEP 2144.04 (II.B) clearly instructs, the omission of an element

and retention of its function is an indicia of unobviousness. *In re Edge*, 359 F.2d 896, 149 USPQ (CCPA 1966). In the present case, the necessary controlled release material, HPMC, as described in the '323 patent, is omitted in the present invention, but the formulation in accordance with the present invention can still attain a desired controlled release profile (see e.g. page 5, lines 1-6 of the specification of the present application). This fact constitutes a ground that the present invention is unobvious over the references cited by the Examiner.

Moreover, as clearly stated by MPEP 2142, the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. Therefore, it is our opinion that Applicants have no obligation to submit evidence showing the criticality of the present invention, as the Examiner proposed in the first paragraph of page 4 of the Office Action dated June 15, 2004.

Additionally, as to the '686 Patent, the Examiner cited the following release rates:

> 30-60% of the Bupropion Hydrochloride after 1 hour,
> 55-80% of the Bupropion Hydrochloride after 2 hours
> 75-95% of the Bupropion Hydrochloride after 3 hours, and
> 80-100% of the Bupropion Hydrochloride after 4 hours.

The current application claims two sets of release rates. Claims 14 and 15 disclose the following release rates:

> 30-45% of the Bupropion Hydrochloride in 1 hour,
> 60-80% of the Bupropion Hydrochloride in 4 hours, and
> not less than 85% in 7 hours.

Claims 16 and 17 disclose the following release rates:

> 10-25% of the Bupropion Hydrochloride in 1 hour,
> 30-60% of the Bupropion Hydrochloride in 8 hours, and

not less than 65% in 12 hours.

As is clearly evident, the release rates of the current invention are slower and more sustained than those of the invention disclosed in the '686 Patent. (This is in addition to the fact that combining any or all of the patents cited as 103 references (the '323, '660, and '686 patents) does not arrive at the invention of the current application. There is no suggestion to use carboxyvinyl polymer as the sole stabilizing agent and the sole controlled release material.)

The Examiner states that lactose and microcrystalline cellulose are disclosed in the specification of the current application as being used for their rate controlling properties. The statement of the specification in question reads: "[t]he present invention also provides for a pharmaceutical composition designed for sustained release (SR) tablets, containing bupropion hydrochloride and carboxyvinyl polymer (Carbopol®) and other pharmaceutically acceptable excipients, preferably lactose and microcrystalline cellulose for controlling the rate of release of the active ingredient for twice a day and once a day dosage regimen." (page 4, lines 7-11). This statement was meant to convey the fact that the pharmaceutical composition as a whole is designed to control the rate of release of the active ingredient, not that the excipients lactose and microcrystalline cellulose were added to control the rate of release. Lactose is used in pharmaceutical compositions as a diluent, not a control release agent. See Rowe, Raymond C. et al., *Handbook of Pharmaceutical Excipients*, p323 (4th ed. 2003) stating under the heading "Functional Category" that lactose is a "[d]iluent for dry-powder inhalers; tablet and capsule diluent." In addition, contrary to the assertion by the examiner that microcrystalline cellulose and HPMC have similar rate controlling properties and can be used interchangeably, microcrystalline cellulose is often used as a disintegrant (which would be useful in an immediate release, rather than a controlled

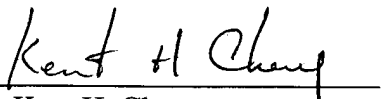
release, formulation). (See Rowe, Raymond C. et al., *Handbook of Pharmaceutical Excipients*, p108 (4th ed. 2003) stating that "[i]n addition to its use as a binder/diluent, microlcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting."). The specification was not meant to teach that a disintegrant should be utilized as a controlled release agent.

As to the Examiner's assertion that there are no examples where carboxyvinyl polymer is used as the sole rate controller or stabilizer since each and every example includes lactose and/or microcrystalline cellulose, this is not valid for two reasons. First, carboxyvinyl polymer is used as the sole rate controller because, as discussed *supra*, the lactose and microcrystalline cellulose are not used to control the rate of release of the active ingredient. Second, the examples are preferred embodiments of the invention and are not meant to so limit the claims.

CONCLUSION

The claims being patentably distinguishable from the art of record, reversal of the final rejection and passage of the case to issue are most earnestly solicited.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

By 

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1. A pharmaceutical composition in solid form comprising bupropion hydrochloride and an effective amount of carboxyvinyl polymer as the sole stabilizing agent and the sole controlled release material.

2. The composition of claim 1, in which the composition contains at least about 90% w/w of undegraded bupropion hydrochloride after storage for 2 weeks at 55^0C.

3. The composition of claim 1, in which the composition contains at least about 90% w/w of undegraded bupropion hydrochloride after storage for 3 months at 40^0C and 75% relative humidity.

4. A pharmaceutical composition according to claim 1, which comprises from about 0.5% to 30% by weight of carboxyvinyl polymer as stabilizer to inhibit the degradation of bupropion hydrochloride.

5. A pharmaceutical composition according to claim 1, which comprises from about 0.5% to 30% by weight of carboxyvinyl polymer to provide drug release over a period of from about 8 hours to about 24 hours.

6. A pharmaceutical composition according to claim 5, which comprises from about 5% to about 30% by weight of the carboxyvinyl polymer.

7. A pharmaceutical composition according to claim 5, which comprises from about 8% to 28% by weight of carboxyvinyl polymer.

8. A pharmaceutical composition according to claim 5, which comprises from about 10% to about 28% by weight of carboxyvinyl polymer.

9. A method of stabilizing bupropion hydrochloride in a pharmaceutical composition according to claim 1, wherein said method comprises mixing bupropion hydrochloride with suitable pharmaceutical excipients and carboxyvinyl polymer and granulating with purified water.

10. A pharmaceutical composition according to claim 1 further comprising a pharmaceutical excipient selected from the group consisting of lactose, magnesium stearate and microcrystalline cellulose.

11. A pharmaceutical composition according to claim 10, wherein the pharmaceutical excipient is microcrystalline cellulose.

12. A sustained release tablet comprising bupropion hydrochloride and carboxyvinyl polymer and lactose, wherein the carboxyvinyl polymer is the sole stabilizing agent and the sole controlled release material.

13. A sustained release tablet comprising bupropion hydrochloride and carboxyvinyl polymer and microcrystalline cellulose, wherein the carboxyvinyl polymer is the sole stabilizing agent and the sole controlled release material.

14. A sustained release tablet according to claim 12, wherein the mean release of bupropion hydrochloride is one of about between 30% and 45% in 1 hour,

about between 60% and 80% in 4 hours, and not less than 85% in 7 hours when tested in distilled water using the United States Pharmacopoeia paddle dissolution method at a rotational speed of 50 rpm.

15. A sustained release tablet according to claim 13, wherein the mean release of bupropion hydrochloride is one of about between 30% and 45% in 1 hour, about between 60% and 80% in 4 hours, and not less than 85% in 7 hours when tested in distilled water using the United States Pharmacopoeia paddle dissolution method at a rotational speed of 50 rpm.

16. A sustained release tablet according to claim 12, wherein the mean release of bupropion hydrochloride is one of about between 10% and 25% in 1 hour, about between 30% and 60% in 8 hours, and not less than 65% in 12 hours when tested in distilled water using the United States Pharmacopoeia paddle dissolution method at a rotational speed of 50 rpm.

17. A sustained release tablet according to claim 13, wherein the mean release of bupropion hydrochloride is one of about between 10% and 25% in 1 hour, about between 30% and 60% in 8 hours, and not less than 65% in 12 hours when tested in distilled water using the United States Pharmacopoeia paddle dissolution method at a rotational speed of 50 rpm.